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SHORT RESEARCH REPORT

Harmful excipients in medicines for neonates in Spain

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Abstract *Background* Neonates may respond differently from adults to drug components. Hence, ingredients that seem safe in adults may not be safe in this age group. *Objective* To describe the content of harmful excipients in drugs used in our neonatal wards and compare the daily dose a neonate may receive with the accepted daily intake (ADI) in adults. *Methods* All drugs included in the hospital's neonatal treatment guide were reviewed, using information from the package inserts or the summary of product characteristics. Those containing at least one harmful excipient (e.g., metabisulfite, sorbitol) were analyzed. Minimum and maximum usual daily drug doses were determined, and excipient exposure was estimated by extrapolation of the minimum and maximum of excipient referred to the active ingredient. These amounts were compared with ADIs for each excipient in adults. *Results* In total, 32 % of intravenous and 62 % of oral formulations used in neonates contained at least one harmful excipient. On quantitative analysis, 25 % of intravenous and 19 % of oral drugs contained harmful excipients exceeding the ADI in adults. *Conclusion* Several drugs commonly used to treat neonates contain harmful excipients in amounts that may exceed the ADI in adults. Clinicians should be aware of this to prescribe appropriate treatment in this population.

Keywords Excipients · Neonatal care · Pediatrics · Spain

Impact of Practice

- Newborns in our neonatal wards and ICU may sometimes receive excessive doses of known to be harmful excipients in the drug formulations they are given.
- It may be advisable to review the drugs commonly given to neonates, seeking alternatives that do not contain or contain smaller amounts of excipients known to be harmful.

Background

Excipients are needed to formulate and assure several properties of a drug preparation, such as solubility, stability, and bioavailability. Because excipients are inert and pharmacologically inactive, it is generally assumed that they are safe for patients, but this may not always be the case. Serious adverse events have been attributed to excipient exposure in drugs, particularly when medications are administered in high doses or to vulnerable population groups [1–3].

Children may not respond to some components of drug formulations in the same way as adults. Neonates are the most vulnerable group within this population, because of organ immaturity and associated differences in the pharmacokinetics and pharmacodynamics of the substances administered [4]. Thus, ingredients that seem to be safe in adults are not necessarily safe in neonates, but drugs developed for adults are commonly used in this patient population.

Regulatory agencies have established criteria to ensure the safety of excipients, and these components should be appropriately evaluated. However, much of the available

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safety data are based on adult exposure [5]. Excipient overexposure is common in neonates, and several reports have suggested that neonates are exposed to systemic concentrations that would not be tolerated in adults [5, 6].

It is important for physicians and pharmacists to be aware of the excipient content of drugs prescribed in the neonatal population, as this may be a decisive factor in selecting the most appropriate agents for treating their patients.

Aim of the study

Our objective was to determine which drugs commonly used in our neonatal wards include harmful excipients and compare the daily dose of these substances a newborn infant may receive with the accepted daily intake (ADI) in adults [7, 8].

Ethical approval

Ethics advisory committee approval was not required for this study.

Methods

Drugs included in the analysis

Two of the authors (BGP, EMP) independently reviewed the following sources to obtain information on excipients considered harmful in neonates: the classification of pharmaceutical excipients proposed by Lass et al. [4], Rowe's Handbook of Pharmaceutical Excipients (6th edition) [8], and the European Medicines Agency (EMA) reflection paper on formulations of choice for the pediatric population [9]. Based on the information obtained and the criteria of the evaluators, excipients considered harmful in neonates and present in oral or parenteral formulations pertinent to our setting were chosen by consensus for the study (Table 1).

The next step was to determine which drugs contained these harmful excipients and how much of each was included in medicines given to neonates. To generate a representative picture of neonatal excipient exposure in our setting, only the medicines included in the hospital's neonatology treatment guide (75 intravenous and 26 oral liquid formulations) were reviewed and analyzed. The qualitative and quantitative compositions of prescription medicines were determined from the package inserts and the summary of product characteristics (SPC), accessed in the European Public Assessment Report (EPAR) database of the EMA. If this information was lacking, the manufacturer was asked to provide data on the exact formulation of their drug.

Data analysis

For each excipient present in the drugs analyzed, we calculated the amount range per milligram in a formulation. First, minimum and maximum usual daily drug doses reported in the hospital's neonatology treatment guide were assessed. Excipient exposure was then estimated by extrapolation of the minimum and maximum daily amounts of excipient referred to the active ingredient.

As there are no available data on the ADIs of excipients in neonates, the results of these calculations were then compared with the ADIs established in the adult population [7, 8]. The daily amount of excipient was considered to exceed the ADI if the minimum or maximum amount of excipient a neonate received in the standard drug doses prescribed was higher than the ADI value.

Summary statistics [mean and standard deviation (SD)] were calculated using Microsoft Office Excel® 2007. Ethics advisory committee approval was not required for this study.

Results

Qualitative analysis

Separate analyses showed that 24/75 (32 %) intravenous formulations and 16/26 (62 %) oral formulations contained at least one harmful excipient; that is, 40 % of the drugs analyzed.

Eleven percent of intravenous drugs contained more than one harmful excipient, with a maximum of five (diazepam injection solution). The most common were sodium metabisulfite, ethanol, and benzyl alcohol, found in seven, six, and four drugs, respectively.

Fifty percent of oral formulations contained two or more excipients under study. The maximum was six (magnesium pidolate and potassium oral suspension), and the most common were parabens (methyl and propyl parahydroxybenzoate) and sorbitol. Parabens were present in seven drugs and sorbitol in five oral formulations.

Quantitative analysis

Comparison of estimated exposure to harmful excipients with the ADIs showed that six (25 %) intravenous formulations contained excipient amounts greater than the adult maximum when administered at doses recommended in neonates. Neonates receiving diazepam injection solution were exposed to higher amounts of propylene glycol than the ADI.

Table 1 Excipients known to be harmful in neonates selected for the study [4, 8, 9]

Class	Excipient		Safety concerns
	E. no.	Name	
Preservatives	E-1519	Benzyl alcohol	Should not be given to neonates due to their immature metabolism: fatal toxic syndrome in premature infants
			Vomiting, diarrhea
			Metabolic acidosis
			Seizures
			Gasping
			Hypersensitivity
	E-210	Benzoic acid	May increase the risk of jaundice in neonate
		Benzoates	
	E-211	Sodium benzoate	
	E-212	Potassium benzoate	
		Parabens	Hyperbilirubinemia in neonates in injection
	E-216	Propyl p-hydroxybenzoate	Hypersensitivity reactions
	E-217	Sodium propyl p-hydroxybenzoate	
	E-218	Methyl p-hydroxybenzoate	
	E-219	Sodium methyl p-hydroxybenzoate	
		Sulfites	Hypersensitivity
	E-223	Sodium metabisulphite	Paradoxical bronchospasm, wheezing, dyspnea
	E-385	Edetate disodium (or disodium EDTA)	Hypocalcemia if used over an extended period of time or if administered too rapidly by intravenous infusion
			Local inflammatory reactions
			Should be used with caution in patients with renal or cardicac impairment
Sweeteners	–	Sucrose	Elevation of blood glucose
			Patients with hereditary fructose intolerance: contraindication
	–	Fructose	Elevation of blood glucose
			Patients with hereditary fructose intolerance: contraindication
			Laxative effects when administered orally
	E-420	Sorbitol	Osmotic diarrhea
			Patients with hereditary fructose intolerance: contraindication
	E-967	Xylitol	Osmotic diarrhea
	E-951	Aspartame	Harmful in patients with phenylketonuria and contraindicated in homozygous autosomal recessive patients
			Hypersensitivity
	E-954	Saccharin and its sodium, calcium and potassium salts	Hypersensitivity reactions
Fillers and solvents	–	Lactose	Patients with lactose intolerance: caution
			Diarrhea, dehydration, metabolic acidosis
	–	Ethanol	Limited metabolic pathway (alcohol dehydrogenase) in children younger than 4 years: depression of the central nervous system
	E-1520	Propylene glycol	Limited metabolic pathway (alcohol dehydrogenase) in children younger than 4 years: depression of the central nervous system
			Laxative effects when administered orally
			Nephrotoxicity
	–	Castor oil	Nausea, vomiting
			Colic, and severe purgation
Dyes	E-102	Tartrazine, FD&C[a] yellow #5	Anaphylactoid reactions: urticaria, angioedema
	E-110	Orange yellow 5, Sunset yellow FCF, FD&C[a] yellow #6	Anaphylactoid reactions: urticaria, angioedema
	E-124	New Coccine, Ponceau 4, Cochineal Red A	Anaphylactoid reactions: urticaria, angioedema
–	–	Gluten	Patients with celiac disease: contraindication
			Should not be given to neonates and infants in the first three months of life

– E number not available

[a] FD&C is a designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics

Metabisulfite, sorbitol, benzyl alcohol, and methyl parahydroxybenzoate exposures were twice the ADI in patients receiving dopamine intravenous solution, gamma globulin intravenous solution, sodium heparin injection solution and naloxone injection solution, respectively. Benzyl alcohol and sodium metabisulfite exposures with administration of epoetin beta solution for injection and dobutamine intravenous solution, respectively, were close to the accepted limit in adults; acceptable limits in neonates have not been defined.

Of 16 oral formulations containing at least one harmful excipient, three (19 %) exceeded the ADI when administered in commonly used doses. The ADI of methyl parahydroxybenzoate was exceeded in loperamide oral solution. The other two drugs: L-carnitine oral solution and acyclovir oral solution contained high amounts of sorbitol. In the oral carnitine solution, sorbitol dose was 293 times the ADI.

Discussion

The availability of safe medicines for neonates is a global concern. Whereas authors in various countries have looked into this issue [4, 6, 10], this is the first study to our knowledge investigating drugs containing harmful excipients administered to neonates in Spain.

The present study has the unavoidable limitation that the calculated excipient exposure was compared with adult ADIs, despite the fact that neonates may not metabolize and eliminate these substances as efficiently as adults. Because of the absence of well-validated prospective studies focusing on this issue in neonates, there are no ADI data for this population. The literature only contains data on the pharmacokinetics of propylene glycol and ethanol in neonates [2, 3], whereas the remaining excipients lack characterization in special populations.

Our study was centered on a theoretical review of the content of harmful excipients in neonates, but it did not define the consequences of administering these substances in daily practice. It would be of considerable interest to evaluate these clinical repercussions in further studies. Considering the total amount of medication a patient receives, the daily intake of various harmful excipients could very well exceed the maximum adult ADIs. Moreover, cumulative intake of these substances over time could lead to a risk of toxicity.

Studies performed in Estonia and Brazil reported higher percentages of drugs (68 and 66.2 % respectively) containing at least one harmful excipient than we found [4, 10]. Although regional characteristics (e.g., products marketed in each country) may have had an influence on these figures, the differences are more likely explained by methodological variations (e.g., drugs included in different neonatology treatment formularies). Regarding quantitative analysis, it is difficult to compare our findings with those of other studies investigating adult ADI cut-offs, as these reports analyzed only a small number of excipients (benzyl alcohol, propylene glycol, ethanol, or sorbitol) [1, 6].

Our results show that neonates are often exposed to potentially toxic excipients that could produce severe and currently undefined consequences. Unfortunately, this issue has not received the attention it merits within neonatal management. It is important for pharmacists to raise the awareness of prescribers in this regard and place emphasis on determining the risk–benefit of each drug. To achieve this goal, it should be mandatory that all SPCs specify the qualitative and quantitative composition of drug formulations. It is also vitally important to optimize our knowledge regarding the clinical safety of drug excipients in neonates to determine whether authorized medications are, indeed, appropriate for this population. At present, there are two ongoing collaborative projects in this line: The Safety and Toxicity of Excipients for Pediatrics (STEP) database and the European Study for Neonatal Excipient Exposure (ESNEE).

Conclusion

Many of the drugs commonly prescribed in neonates contain excipients known to be harmful in this specific population, and some excipients are present in amounts that exceed the ADI in adults. The long-term effects of this practice, directly related to the dose or duration of exposure, are unknown.

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Conflicts of interest None.

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